Efficacy of intravitreal pegcetacoplan in patients with geographic atrophy (GA): 18-month results from the phase 3 OAKS and DERBY studies

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Disclosures

- Roger Goldberg has the following financial interests or relationships to disclose:
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  - Equity: Emmetrope Ophthalmics
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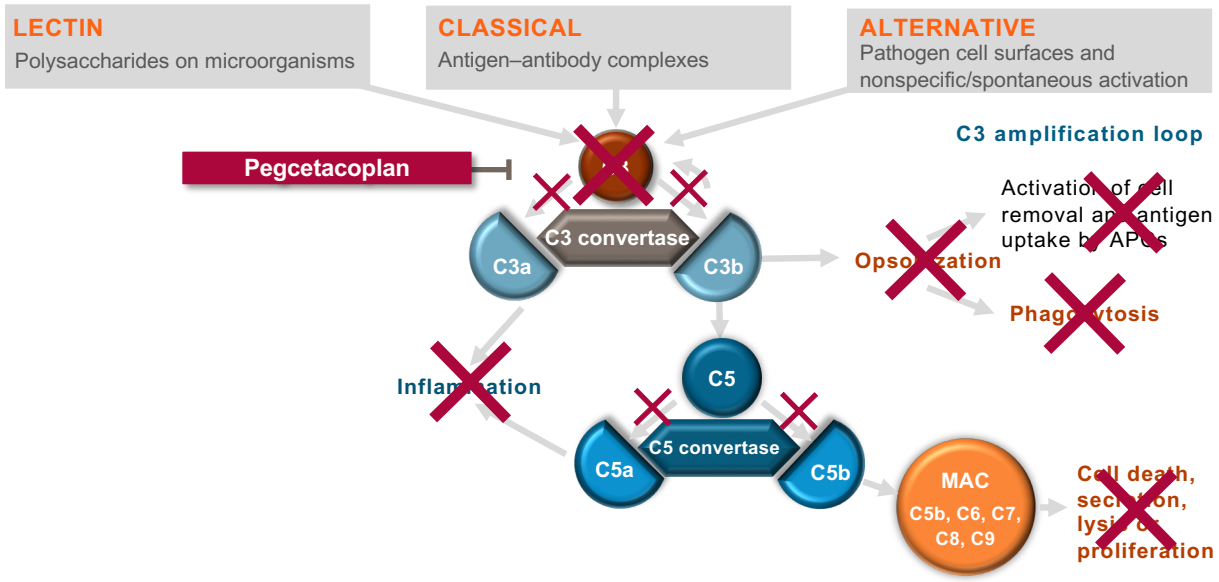
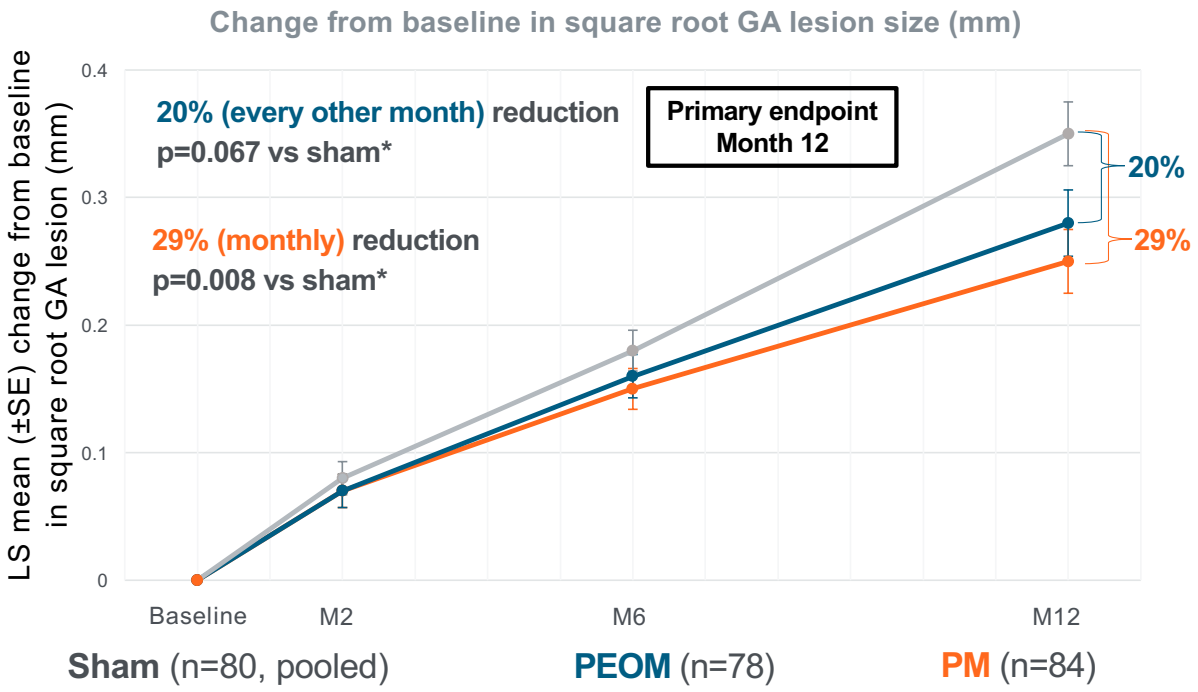
Inhibition of the complement cascade provides a therapeutic target for GA



- Dysregulation of the complement cascade has been implicated in GA pathogenesis
- All 3 complement pathways end in the central cleavage of C3
- Pegcetacoplan is a 44 kDa pegylated highly-selective bi-cyclic peptide conjugated to a PEG polymer
- Inhibition of C3 blocks steps in the complement cascade needed for opsonization, inflammation, and formation of MAC

Figure adapted from Ricklin D, et al. *Immunol Rev*. 2016;274:33–58.
APC=antigen-presenting cell; GA=geographic atrophy; MAC=membrane attack complex.
Liao DS, et al. *Ophthalmology*. 2020;127:186–95.

Phase 2 FILLY results



- In the Phase 2 FILLY trial, pegcetacoplan resulted in statistically significant reductions in the growth of GA versus sham over 12 months, meeting the primary endpoint
- **Phase 3 DERBY & OAKS objective:** to assess the efficacy and safety of multiple intravitreal injections of pegcetacoplan in patients with GA secondary to AMD

*p<0.1 was the predefined threshold for statistical significance in FILLY.
AMD=age-related macular degeneration; GA=geographic atrophy; LS=least square; M=Month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
Liao DS, et al. *Ophthalmology*. 2020;127:186–95.

Global phase 3 program: Design of studies (OAKS & DERBY)

OAKS DERBY

Patients with GA secondary to AMD
~600 patients at ~200 sites globally in 2 studies (1,258 enrollees total)

APL-2 303 (DERBY)
CT.gov identifier:
NCT03525600

APL-2 304 (OAKS)
CT.gov identifier:
NCT03525613

Double-masked

Randomized 2:2:1:1

Pegcetacoplan 15 mg/0.1 mL monthly	Pegcetacoplan 15 mg/0.1 mL EOM	Sham monthly	Sham EOM

Analysis Month 18

Primary endpoint at 12 months
Change in total area of GA lesions based on fundus autofluorescence

End of study at 24 months

- BCVA, LL-BCVA, low-luminance deficit
- Reading speed
- NEI VFQ-25
- FRI Index composite score
- Microperimetry (OAKS only) – Macular Integrity Assessment (MAIA) device

GALE open-label extension study (3 years)

APL-2 305 (GALE)
CT.gov identifier:
NCT04770545

AMD=age-related macular degeneration; BCVA=best corrected visual acuity; CNV=choroidal neovascularization; EOM=every other month; FRI=functional reading index; GA=geographic atrophy; LL=low luminance; MMRM=mixed-effect model for repeated measures; NEI-VFQ=National Eye Institute Visual Function Questionnaire-25.

18 MONTHS

Key demographics and baseline study eye characteristics

OAKS

Characteristic		PM (N=202)	PEOM (N=205)	Sham Pooled (N=207)
Age, mean (SD)		78.8 (7.24)	78.1 (7.74)	78.6 (7.25)
Female, n (%)		125 (61.9%)	117 (57.1%)	133 (64.6%)
Male, n (%)		77 (38.1%)	88 (42.9%)	73 (35.4%)
Geographic region				
USA, n (%)		147 (72.8%)	142 (69.3%)	148 (71.5%)
ROW, n (%)		55 (27.2%)	63 (30.7%)	59 (28.5%)
Caucasian, n (%)		185 (91.6%)	189 (92.2%)	188 (90.8%)
GA lesion size (mm^2), mean (SD)		8.18 (3.895)	8.30 (3.904)	8.21 (3.712)
Square root GA lesion size (mm), mean (SD)		2.78 (0.682)	2.80 (0.674)	2.79 (0.647)
GA lesion size, n (%)	<7.5 mm^2	101 (50.0%)	98 (47.8%)	104 (50.2%)
GA lesion location, n (%)	Extrafoveal	86 (42.6%)	74 (36.1%)	60 (29.0%)
GA lesion focality, n (%)	Unifocal	59 (29.2%)	62 (30.2%)	68 (32.9%)
Intermediate/large drusen, n (%)	>20	93 (46.0%)	104 (50.7%)	104 (50.2%)
Fellow eye CNV, n (%)		43 (21.3%)	37 (18.0%)	43 (20.8%)
Study eye pseudodrusen (NIR), n (%)		167 (82.7%)	178 (86.8%)	173 (83.6%)
NL-BCVA (ETDRS letters), mean (SD)		61.0 (15.30)	58.2 (17.03)	57.6 (16.59)

These analyses were performed on the Month 18 modified intent-to-treat (mITT) population. The mITT population was defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 post-baseline value of GA lesion area in the study eye.

ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; mm=millimeters; n=number of patients; NL-BCVA=normal luminance best-corrected visual acuity; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; ROW=rest of world; SD=standard deviation.

Key demographics and baseline study eye characteristics

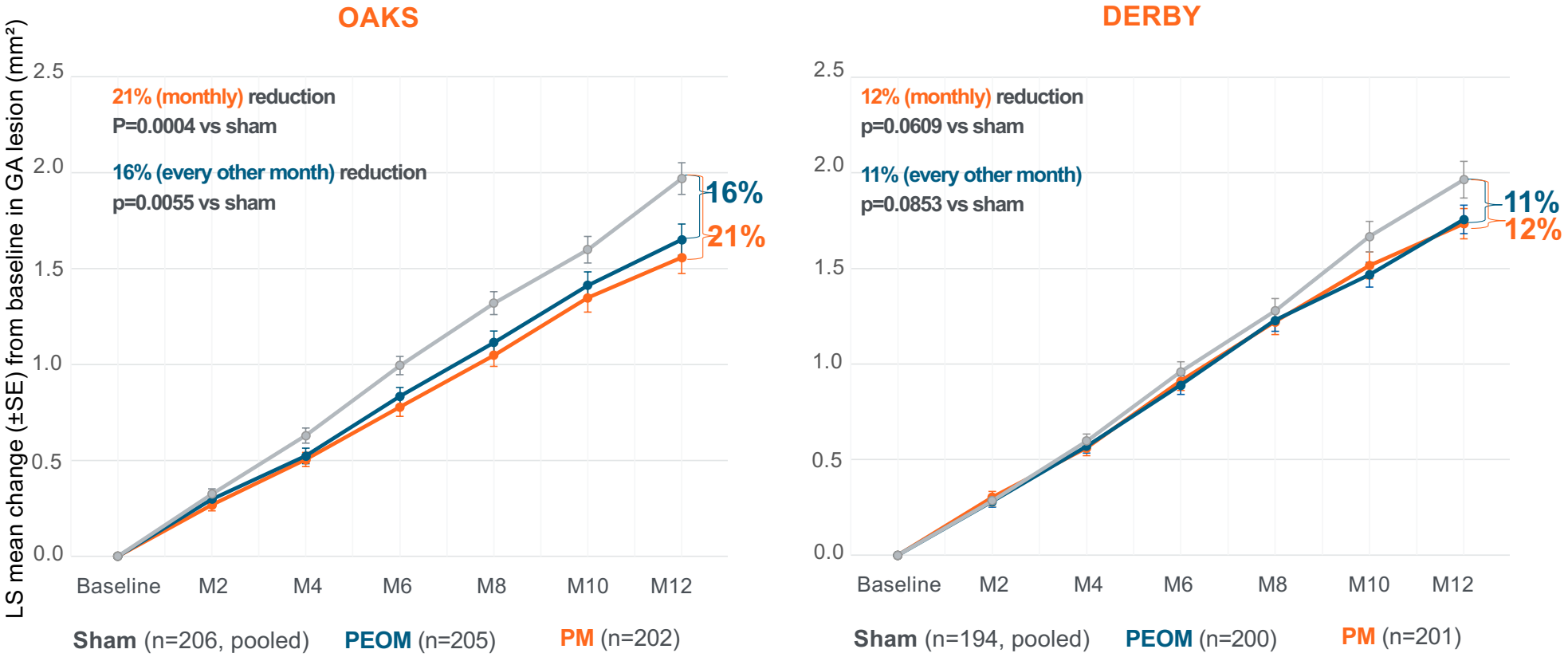
DERBY

Characteristic		DERBY PM (N=201)	DERBY PEOM (N=201)	Sham Pooled (N=195)
Age, mean (SD)		78.7 (6.91)	79.2 (7.08)	78.6 (7.28)
Female, n (%)		118 (58.7%)	120 (59.7%)	123 (63.1%)
Male, n (%)		83 (41.3%)	81 (40.3%)	72 (36.19%)
Geographic region				
USA, n (%)		142 (70.6%)	122 (60.7%)	122 (62.6%)
ROW, n (%)		59 (29.4%)	78 (39.3%)	73 (37.4%)
Caucasian, n (%)		187 (93.0%)	186 (92.5%)	188 (96.4%)
GA lesion size (mm^2), mean (SD)		8.37 (4.181)	8.25 (3.894)	8.24 (4.261)
Square root GA lesion size (mm), mean (SD)		2.80 (0.722)	2.79 (0.678)	2.78 (0.734)
GA lesion size, n (%)	<7.5 mm^2	99 (49.3%)	98 (48.8%)	95 (48.7%)
GA lesion location, n (%)	Extrafoveal	72 (35.8%)	81 (40.3%)	73 (37.4%)
GA lesion focality, n (%)	Unifocal	54 (26.9%)	53 (26.4%)	66 (33.8%)
Intermediate/large drusen, n (%)	>20	78 (38.8%)	78 (38.8%)	98 (50.3%)
Fellow eye CNV, n (%)		39 (19.4%)	41 (20.4%)	36 (18.5%)
Study eye pseudodrusen (NIR), n (%)		178 (88.6%)	181 (90.0%)	166 (85.1%)
NL-BCVA (ETDRS letters), mean (SD)		59.5 (17.40)	58.7 (16.12)	59.0 (16.85)

These analyses were performed on the Month 18 modified intent-to-treat (mITT) population. The mITT population was defined as all randomised patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 post-baseline value of GA lesion area in the study eye.

ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; mm=millimeters; n=number of patients; NL-BCVA=normal luminance best-corrected visual acuity; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; ROW=rest of world; SD=standard deviation.

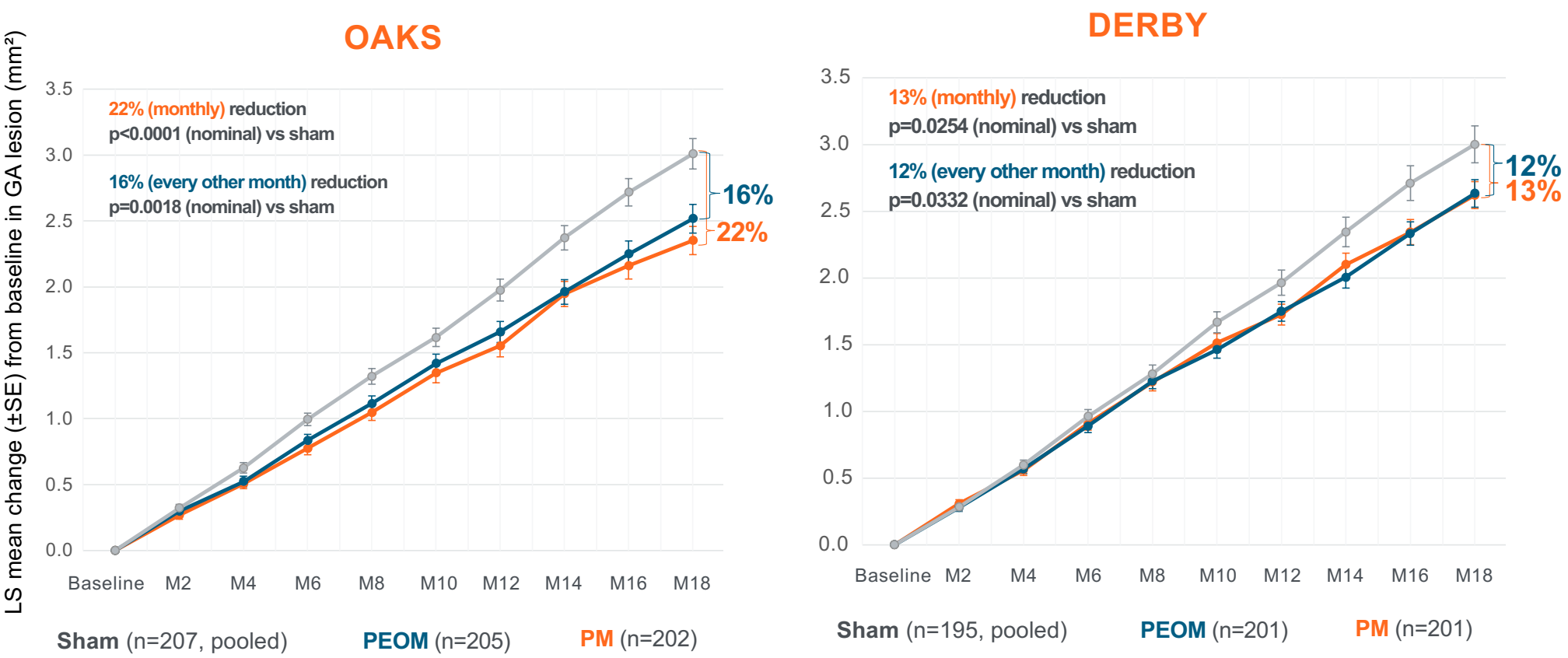
At **Month 12**, Pegcetacoplan monthly and every other month met the primary endpoint in **OAKS** but not **DERBY**



LS means estimated from a mixed-effects model for repeated measures (MMRM). The modified intention-to-treat population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 post-baseline value of GA lesion area in the study eye.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Pegcetacoplan reduced GA lesion growth vs sham in **OAKS** and **DERBY** at **Month 18**

OAKS DERBY



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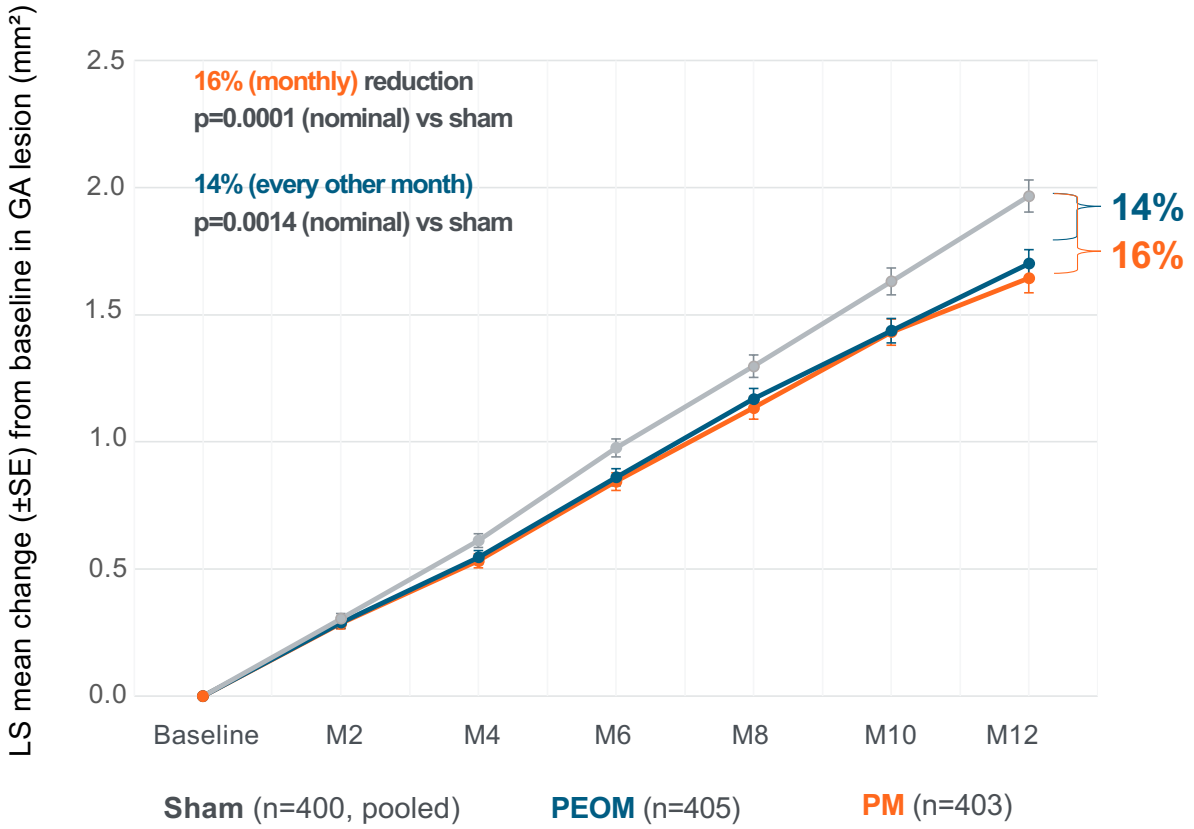
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

In the combined analysis, pegcetacoplan reduced GA lesion growth vs sham at **Month 12**



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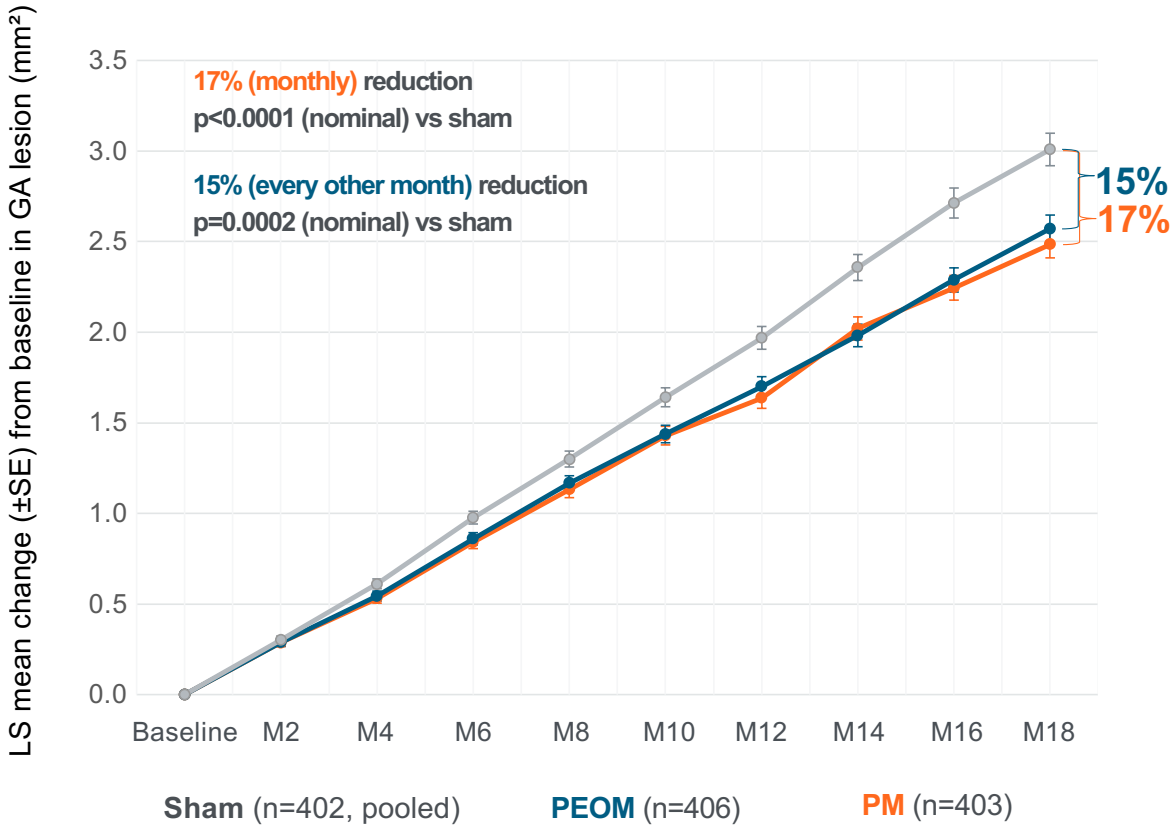
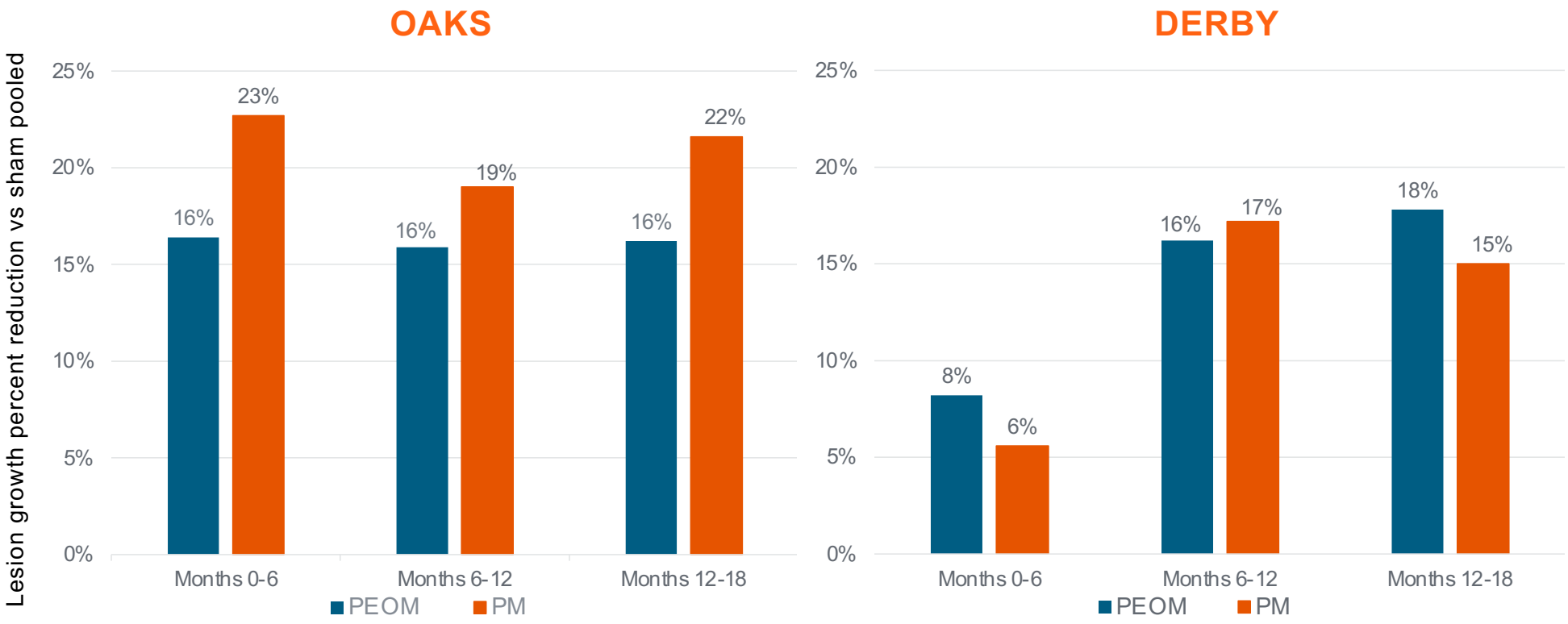
In the combined analysis, pegcetacoplan reduced GA lesion growth vs sham at **Month 18**



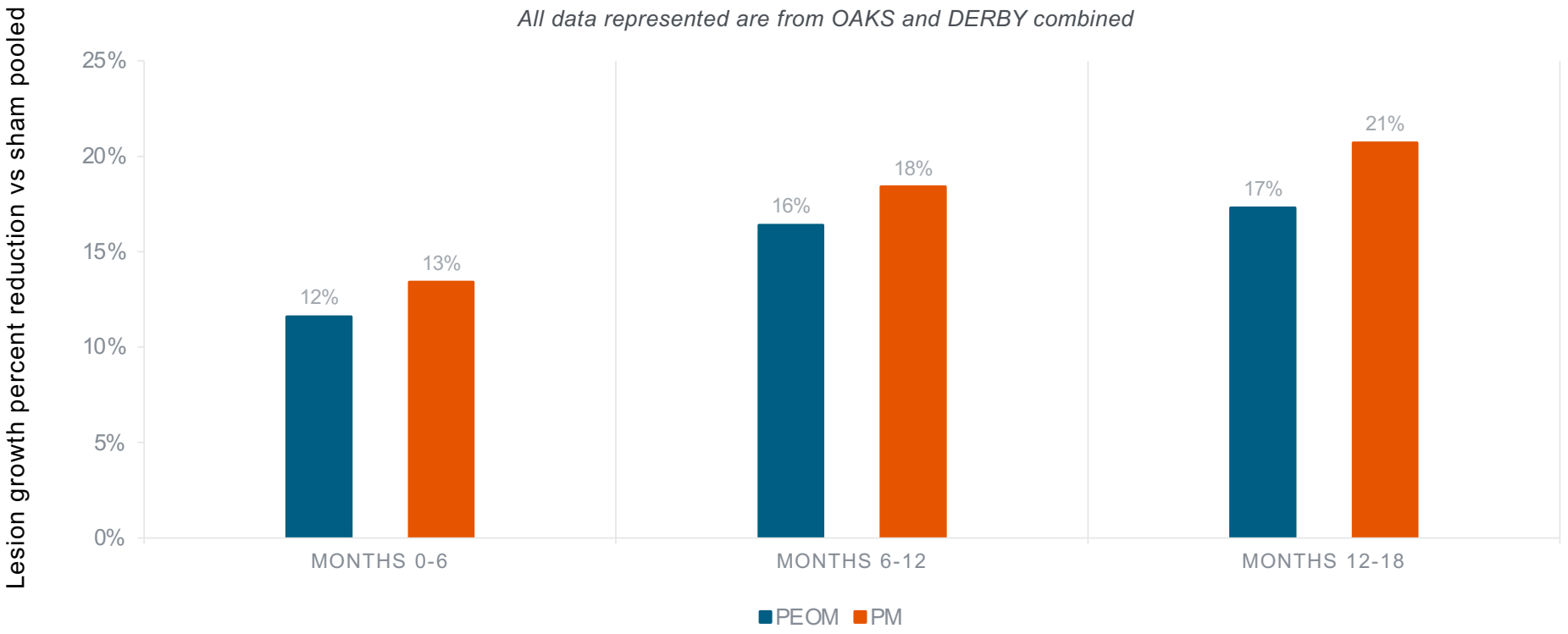
GA=geographic atrophy; LS=least squares; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

Reductions in GA lesion growth in OAKS and DERBY over 6-month periods from baseline to **Month 18**



Percent reduction vs. sham pooled for Month 0 to Month 18 was estimated from a piecewise linear slope model with 6-month segments.
GA=geographic atrophy; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

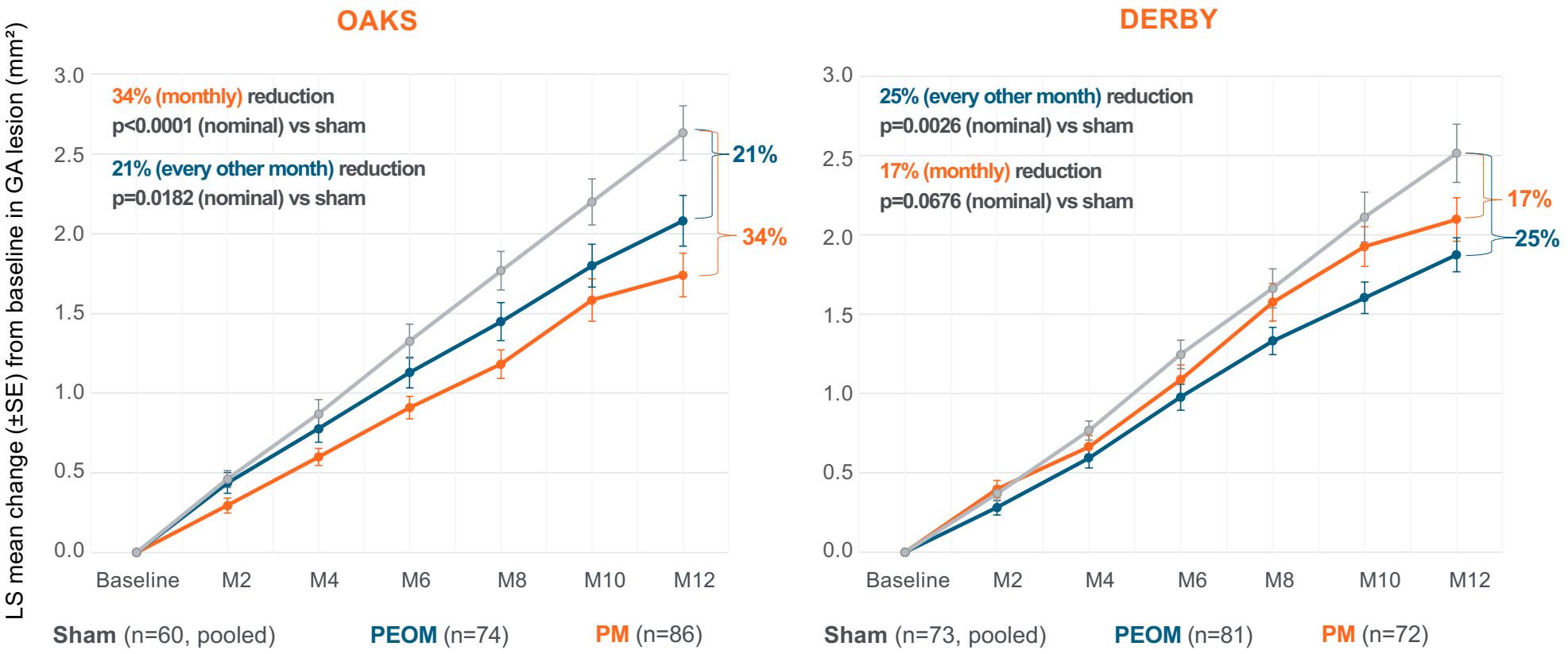
Reductions in GA lesion growth in **OAKS and DERBY combined** over 6-month periods from baseline to **Month 18**



Percent reduction vs. sham pooled for Month 0 to Month 18 was estimated from a piecewise linear slope model with 6-month segments.
GA=geographic atrophy; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

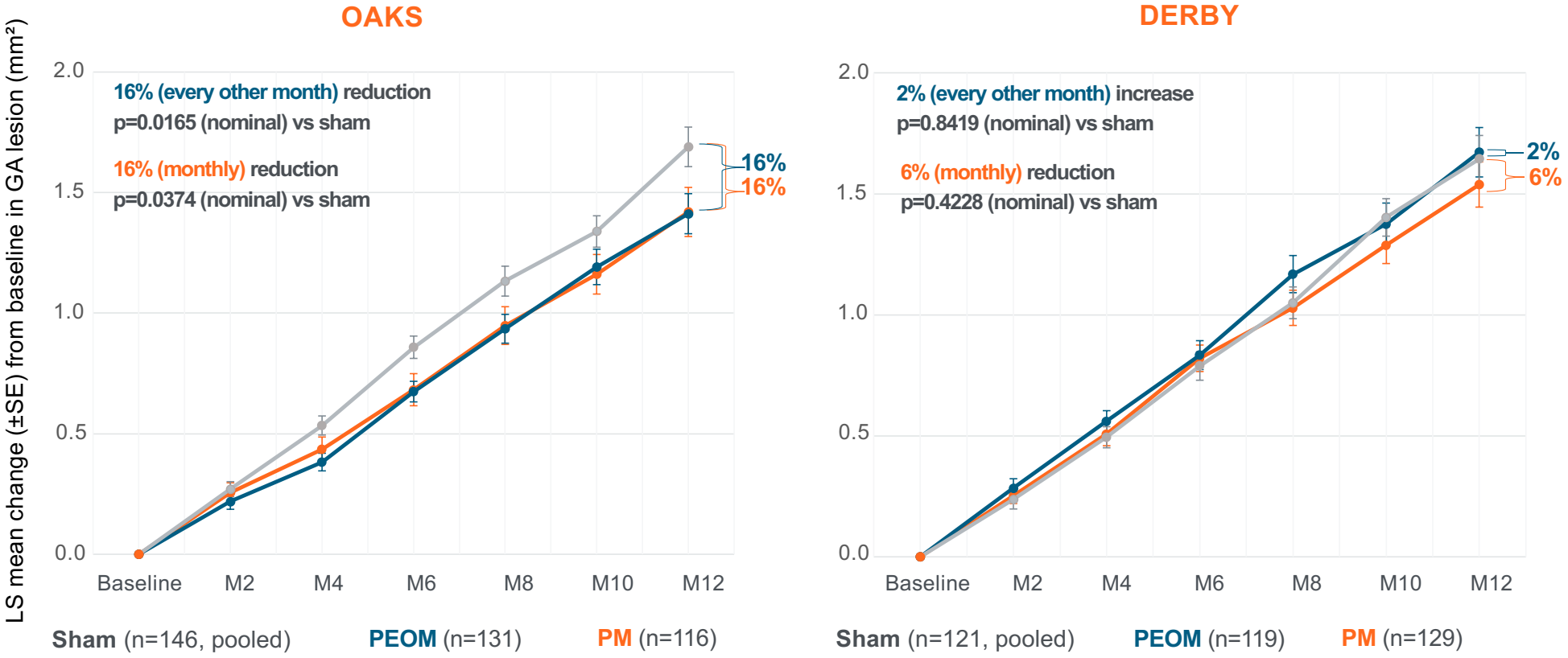
Pegcetacoplan reduced lesion growth in patients with **extrafoveal** lesions in a prespecified analysis at **Month 12**

OAKS DERBY



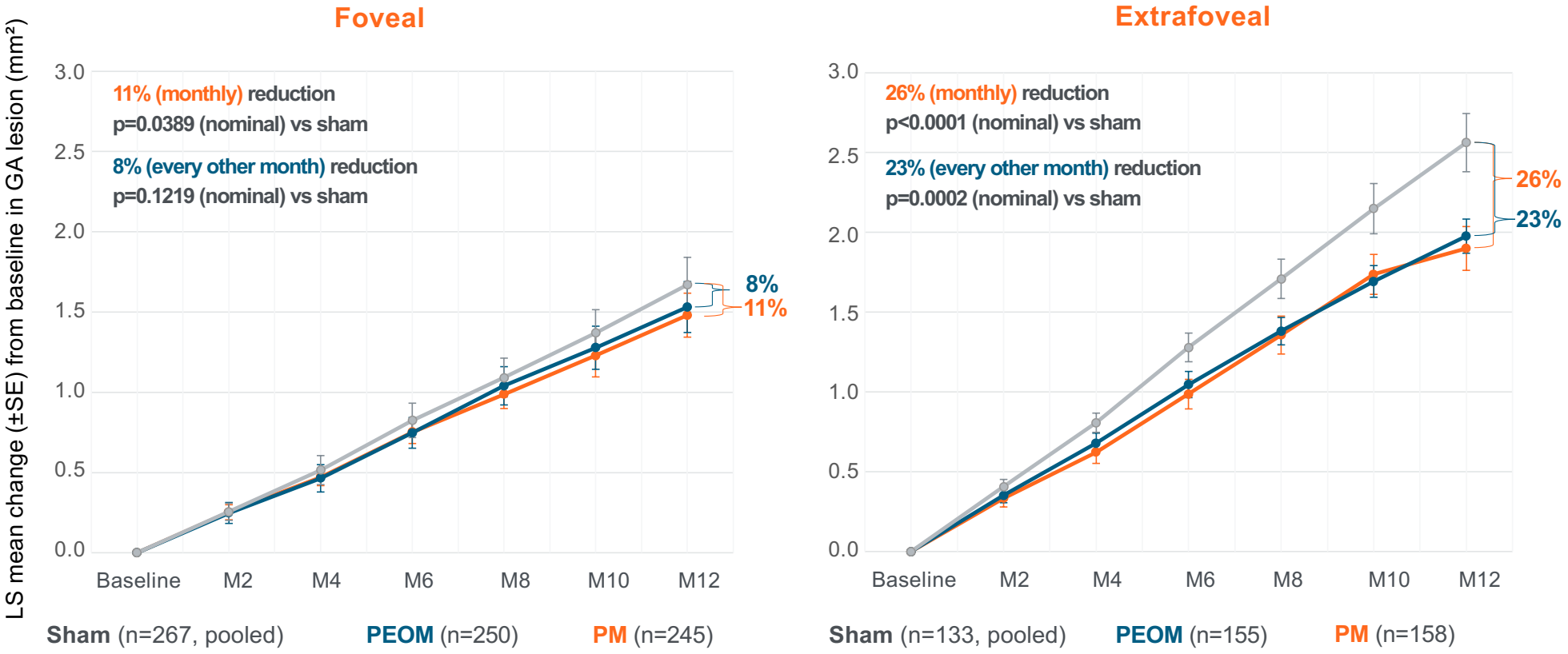
Extrafoveal is defined as lesion with distance >0 to foveal center point.
LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Pegcetacoplan reduced lesion growth in **foveal** lesions in **OAKS** in a prespecified analysis at **Month 12**



Foveal was defined as lesion edge within center point of the fovea.
LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

In the combined analysis, pegcetacoplan reduced **foveal** and **extrafoveal** lesion growth at **Month 12**



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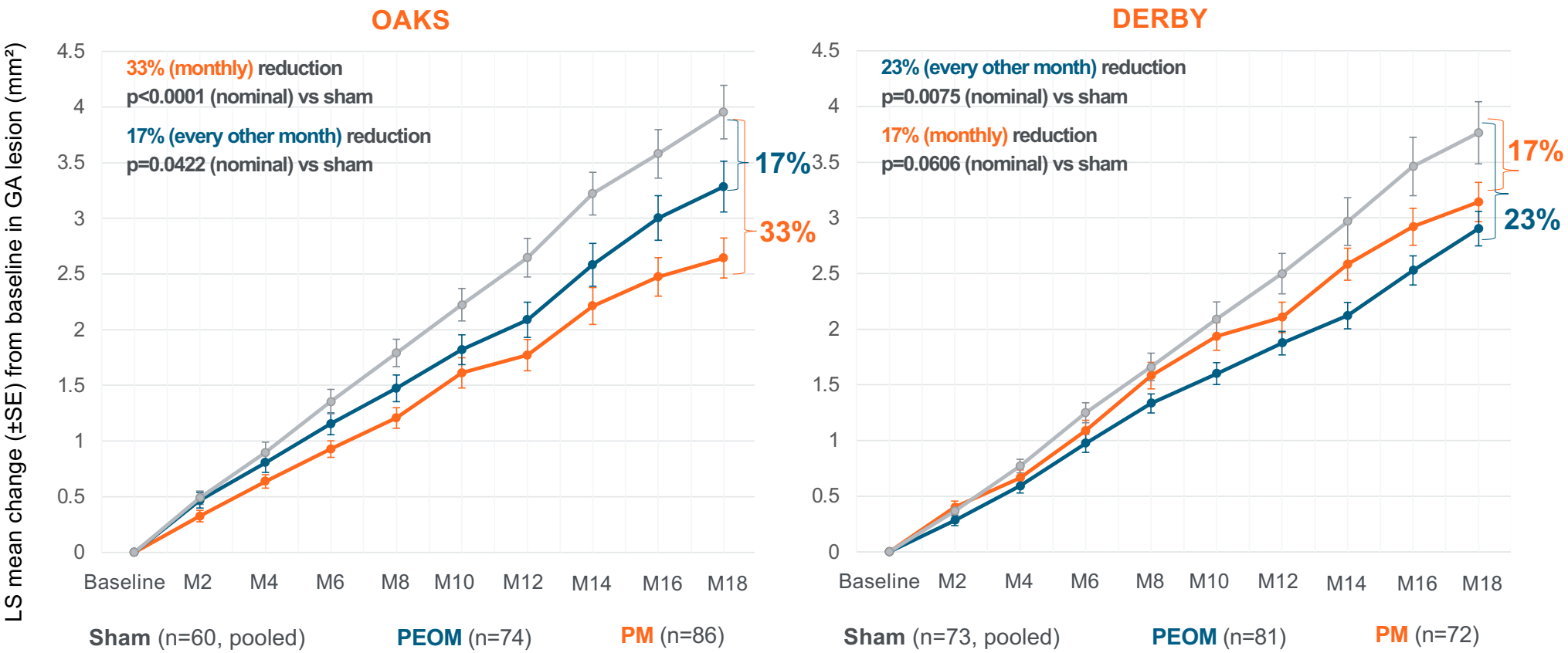
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Pegcetacoplan continued to show reduced lesion growth in patients with **extrafoveal** lesions **at Month 18**

OAKS DERBY

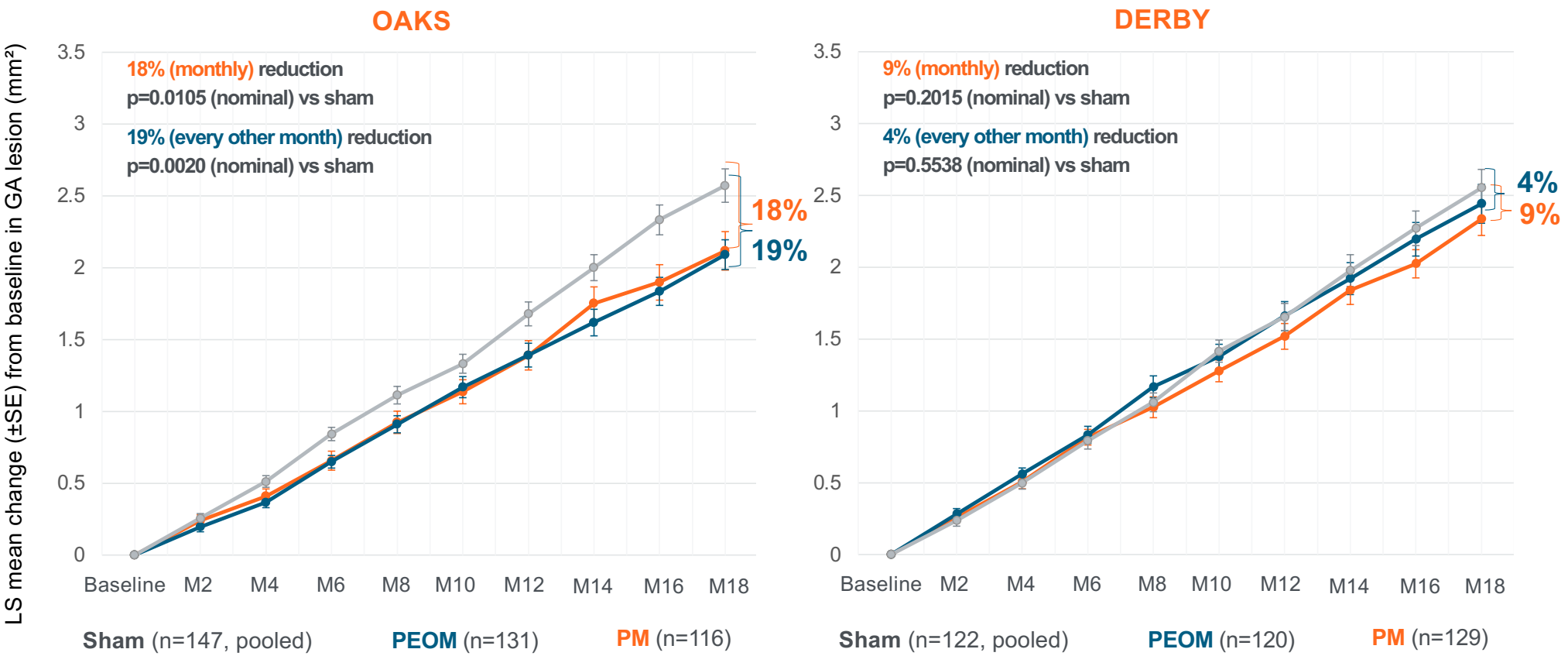


Extrafoveal is defined as lesion with distance >0 to foveal center point.

LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.

GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Pegcetacoplan reduced lesion growth in patients with **foveal** lesions at **Month 18**



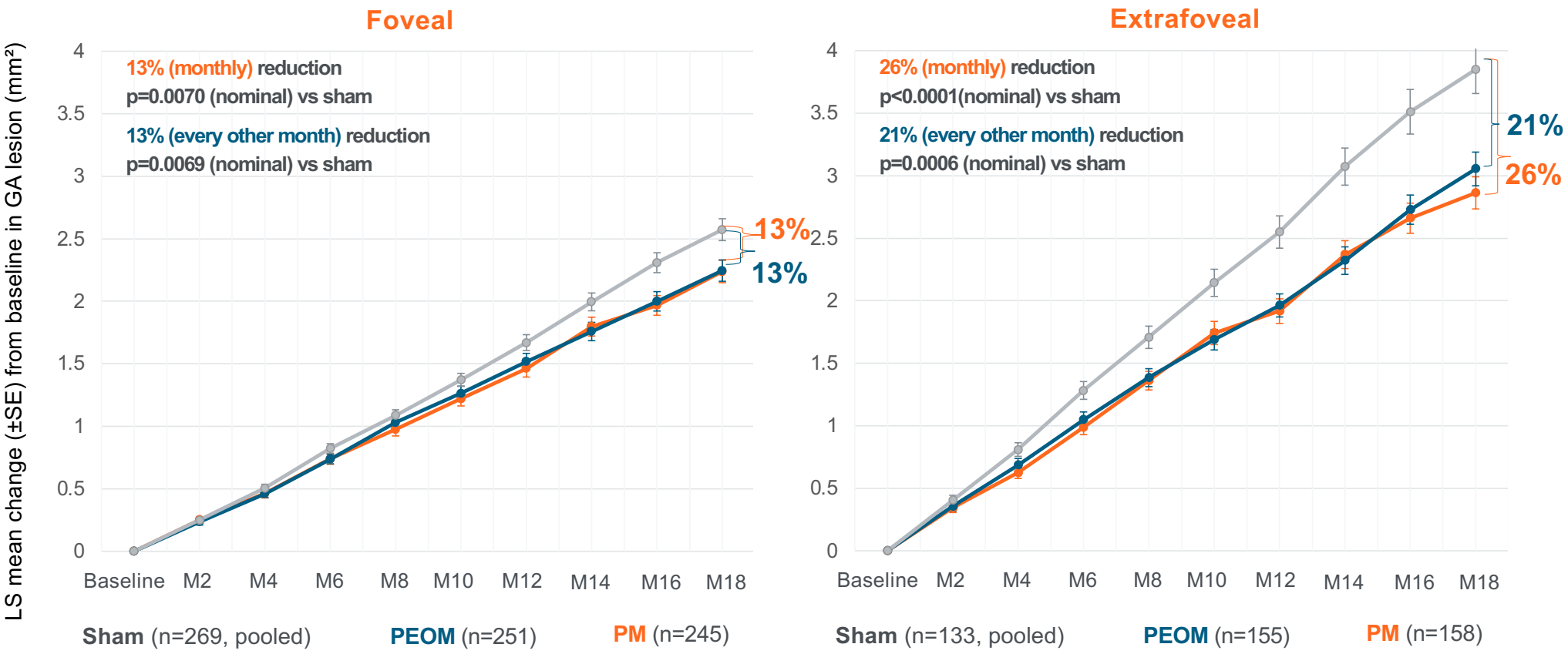
Foveal was defined as lesion edge within center point of the fovea.

LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.

GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

In the combined analysis, pegcetacoplan reduced **foveal** and **extrafoveal** lesion growth at **Month 18**

OAKS DERBY



Foveal was defined as lesion edge within center point of the fovea.

LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.

GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

18 Month Safety

Overall TEAEs at 18 months

Note: Sham patients do not receive injections

OAKS DERBY

	OAKS			DERBY		
	PM (N=213)	PEOM (N=212)	Sham Pooled (N=211)	PM (N=206)	PEOM (N=208)	Sham Pooled (N=206)
All TEAEs, n (%)	185 (86.9%)	177 (83.5%)	169 (80.1%)	170 (82.5%)	171 (82.2%)	164 (79.6%)
Total events, M	1037	965	893	993	835	734
Ocular TEAEs in study eye						
Patients, n (%) M	126 (59.2%) 325	114 (53.8%) 270	88 (41.7%) 199	118 (457.3%) 308	99 (47.6%) 216	84 (40.8%) 151
Non-ocular TEAEs						
Patients, n (%) M	152 (71.4%) 573	158 (74.5%) 567	144 (68.2%) 559	148 (71.8%) 567	132 (63.5%) 495	131 (63.6%) 485
Serious ocular TEAEs in the study eye, n (%) M	5 (2.3%) 5	4 (1.9%) 4	0	4 (1.9%) 4	0	2 (1.0%) 2
Optic ischemic neuropathy	2 (0.9%) 2	0	0	1 (0.5) 1	0	0
Papilledema	1 (0.5%) 1	0	0	0	0	0
Retinal tear	0	0	0	1 (0.5) 1	0	0
Retinal detachment	0	1 (0.5%) 1	0	0	0	0
Endophthalmitis[a]	2 (0.9%) 2	3 (1.4%) 3	0	0	0	0
Vitritis	0	0	0	2 (1.0%) 2	0	0
Dry AMD	0	0	0	0	0	1 (0.5%) 1
Macular hole	0	0	0	0	0	1 (0.5%) 1

[a]The events of endophthalmitis include infectious and noninfectious endophthalmitis.

Any AEs with missing or unknown severity were considered as severe. The safety population was used for this analysis.

AE=adverse event; AMD=age-related macular degeneration; M=number of events; n=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; TEAE=treatment-emergent AE.

eAMD findings from FILLY informed the design of the Phase 3 program

OAKS DERBY

- If eAMD suspected by the Investigator, prespecified imaging (CFP, OCT, FA & OCTA [select sites]) captured
- Patients remain on study treatment and also treated with anti-VEGF pharmacotherapy per protocol
  - Initiation of anti-VEGF therapy for eAMD is at the discretion of the investigator and is not reading-center determined
- Within the reporting from OAKS and DERBY
  - Reports of eAMD include all adverse events reported by the investigator falling within the preferred terms neovascular AMD or CNV, regardless of reading center confirmation

AMD=age-related macular degeneration; CFP=color fundus photography; CNV=choroidal neovascularization; eAMD=exudative AMD; FA=fundus autofluorescence; OCT=optical coherence tomography; OCTA=OCT angiography; VEGF=vascular endothelial growth factor.

Investigator-reported events of eAMD at Month 18[a]

COMBINED STUDIES	PM (N=419)	PEOM (N=420*)	Sham Pooled (N=417)
Investigator-determined new-onset eAMD, %	40 (9.5%)	26 (6.2%)	12 (2.9%)
Rate of eAMD per 100 patient-years			
Month 12	6.6	4.4	2.6
Month 18	7.4	4.6	2.2

- Investigator-determined new-onset eAMD at Month 12 was reported in 6.0%, 4.1%, and 2.4% of patients in PM, PEOM, and sham, respectively
- Additional cases of MNV were detected by reading center on Month 12 FA (2 PM, 4 PEOM, and 6 sham pooled) and the next protocol-specified FA is at Month 24
- Majority of events were classified as occult/Type 1 MNV on FA taken at time of exudation

[a]Events include preferred terms of choroidal neovascularization and neovascular AMD.
*One patient had CNV on medical history in study eye and is not counted in the denominator for this analysis. 211 patients were at risk of new-onset eAMD.
AE=adverse event; AMD=age-related macular degeneration; eAMD=exudative AMD; FA=fluorescein angiography; MNV=macular neovascularization; n=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan every month.

Safety profile of pegcetacoplan in DERBY and OAKS (pooled) at 18 months

OAKS DERBY

- **Intraocular inflammation:**
  - Over 18 months, 21 events of intraocular inflammation were observed in 18 patients. The rate of intraocular inflammation was 0.23% per injection (as compared to 14 events in 13 patients and 0.22% per injection at month 12).
    - This total includes four cases that were reported in 2018 and linked to a drug impurity, one of which was an event of non-infectious endophthalmitis. The rate of intraocular inflammation over 18 months was 0.19% per injection if these four 2018 cases attributable to drug impurity from the 2018 drug lot are excluded
- **Infectious endophthalmitis:**
  - There were 4 cases of infectious endophthalmitis across the PM and PEOM arms
    - 2 confirmed, 2 suspected
    - 0.044% per injection (9,145 total injections)
- **Additional:**
  - No cases of retinitis or vasculitis (occlusive or nonocclusive) were reported

eAMD=exudative age-related macular degeneration; IOI=intraocular inflammation; IP=investigational product; IVT=intravitreal; PEOM=pegcetacoplan every other month; PPV=pars plana vitrectomy; PM=pegcetacoplan monthly; VEGF=vascular endothelial growth factor.

Conclusions

OAKS DERBY

- Pegcetacoplan showed continued reductions in lesion growth from baseline to Month 18 in both studies (all nominal p-values < 0.05)
- Pegcetacoplan demonstrated efficacy in patients with foveal and extrafoveal lesions
- Pegcetacoplan was well-tolerated through Month 18
  - 9.5%, 6.2%, and 2.9% of patients in the combined PM, PEOM, and sham groups experienced new-onset investigator-determined eAMD over 18 months
  - Patients who developed eAMD continued treatment with pegcetacoplan and received anti-VEGF therapy
  - Rate of IOI was 0.23% per injection
  - Rate of infectious endophthalmitis was 0.044% per injection, in line with previous prospective pivotal trials of intravitreal therapeutics
- The pegcetacoplan GA development program includes over 1,500 patients across OAKS, DERBY, and FILLY, collectively demonstrating slowing of GA progression by pegcetacoplan monthly and every other month

GA=geographic atrophy.